REMARKS

Claims 89-128 are currently pending in the present application.

Specification Amendments:

The Specification has been amended to correct an inadvertent typographical error in the paragraph bridging pages 88-89. The reagent "5 mM maleimide-PEG5k" has been replaced with "5 mM Mal-PEG5k." As indicated at line 22 of page 92, the abbreviation "Mal" represents a maleimidopropionyl moiety. The correction now brings the synthesis described in the paragraph bridging pages 88-89 into conformance with the structures shown as compounds 62 and 63. The amendment is supported by the structures of compounds 62 and 63. No new matter is introduced. Entry of the amendment to the Specification is respectfully requested.

Claim Amendments:

Claims 89-98 and 122 have been amended. Claim 89 has been amended to remove "[Activity Moiety]" from the general formula and replace it with the designation "[T]" which can represent D or A, wherein D represents an amine-containing biologically active moiety and A represents a leaving group. Claims 90-98 have been amended in conjunction with the amendment to claim 89 to properly refer back to the language used in amended claim 89. Claim 122 has been amended to correct a duplication of molecular structures. Support for the amendments to the claims can be found in the Specification, for example, at pages 14-17, at page 26, lines 11-31, and in the original claims. The amendments made herein introduce no new matter. Additionally, a complete listing of all claims ever presented is set forth in accordance with 37 CFR §1.121(c)(1). Entry and consideration of the amendments made herein are respectfully requested.

Restriction Requirement:

In the Office Action, the Examiner acknowledges the election of Group I and the species embodied by Compound 63. In the Office Action, the Examiner contends that claims 94, 97-98 and 110-113 do ***not*** read on the elected species, and has withdrawn these claims from

consideration. Applicants respectfully disagree and submit that claims 94, 97-98 and 110-113 do read on the elected species. More specifically, with respect to claims 94 and 97-98, each of these dependent claims recites "somatropins" among the Markush group of biologically active moieties. As clearly indicated in the Specification at page 19, line 3, and as understood by those of ordinary skill in the art, "somatropins" refer to growth hormones. Accordingly, the "rHGH" of the elected species falls within the recited term "somatropins." Thus, claims 94 and 97-98 read on the elected species. With respect to claims 110 and 111, each of these dependent claims recites "maleimide" as a functional group of R1 for linkage to X. As disclosed in the Specification, the disulfide of compound 62 is reacted with a maleimide group of R1 to form an S-succinimide linkage in compound 63. Claims 112 and 113 recite an S-succinimide linkage as the bond between the functional group of R1 and X. Accordingly, claims 110-113 all read on the elected species. Rejoinder and reconsideration of claims 94, 97-98 and 110-113 are respectfully requested.

Objections to the Specification:

In the Office Action, the Examiner has objected to the Specification, contending that the method of synthesis and the structure of Compound 63 are not in agreement. Applicants have amended the Specification to correct the text describing the synthesis of Compound 63. The reagent employed is now correctly recited as "5 mM Mal-PEG5k." As indicated at line 22 of page 92, the abbreviation "Mal" represents a maleimidopropionyl moiety. Removal of the objection is respectfully requested.

Rejections under 35 U.S.C. §112:

In the Office Action, the Examiner rejects claims 89 and 91 under 35 U.S.C. §112, second paragraph, as being indefinite. The claims have been amended to delete the term "[Activity Moiety]". The rejection in that regard is rendered moot. With respect to the term "polymeric cascade prodrug . . .", Applicants respectfully traverse the Examiner's rejection. Applicants submit that it is clear from the Specification that the term "polymeric" refers to the "Carrier" portion of the claimed prodrugs and reagents. At page 4, lines 21-24 of the

Specification, a polymeric cascade prodrug is defined as containing a temporary linkage with a transient *polymeric* carrier group. Applicants submit that the carrier is polymeric. Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. §102(b):

In the Office Action, the Examiner rejects claims 89, 91-93 and 95 under 35 U.S.C. §102(b), as being anticipated by International Patent Publication No. 99/30727 of Greenwald, *et al.* ("Greenwald"). Applicants respectfully traverse the Examiner's rejection and the arguments and contentions set forth in support thereof for at least the following reasons.

Various embodiments of the present invention are directed to prodrugs of the the general formula: [Masking Group] - [Carrier] - [D]. Prodrugs of this formula release three moieties: a Masking Group moiety, a Carrier moiety and a moiety D. Thus, in such prodrugs, upon release, the Masking Group is different from the Carrier, i.e. the Masking Group is non-polymeric. The Carrier moiety is polymeric.

In contrast to the present invention, Greenwald discloses prodrugs which have the general formula (II):

[Carrier - Masking Group] - [X] - [D] (II).

The prodrugs of Greenwald also release three moieties, namely (i) a Carrier-Masking Group conjugate, (ii) a moiety X and (iii) a moiety D. Thus, the Masking Group conjugate of Greenwald's prodrugs is always polymeric.

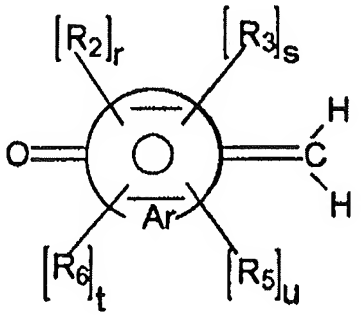
Accordingly, the prodrugs of the present invention are different from the prodrugs of Greenwald and are not anticipated by Greenwald. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejections under 35 U.S.C. §103(a):

In the Office Action, the Examiner rejects claims 89-93, 95, 99, 101-102, 115-116, 118-120 and 122-124 under 35 U.S.C. §103(a), as being obvious over Greenwald in view of the 2003 Amir, *et al.* article in ANGEW CHEM. INT. ED., U.S. Patent Publication No. 2004/0038892 of Finn, *et al.* and the 2001 Veronese article in BIOMATERIALS. Applicants

respectfully traverse the Examiner's rejection and the arguments and contentions set forth in support thereof for at least the following reasons.

In Greenwald, the polymeric moiety (R11) is in a different position than the polymeric moiety (R1) of the present invention. Upon degradation of the Greenwald prodrug, a small aromatic molecule is released, such as the moiety that is for example shown on page 14 of Greenwald:

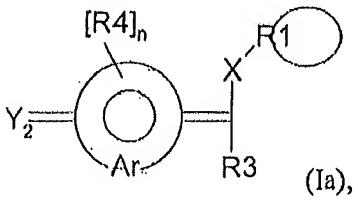


wherein R_2, R_3, R_5, R_6, r, s, t, and u are used as in Greenwald (none of these variables is the polymer).

The small aromatic molecule released from the Greenwald prodrugs is potentially toxic and thus its release in a patient's body is highly undesirable. As these potentially toxic small aromatic molecules are released in a 1:1 stoichiornetry with the drug, high levels of this unwanted and dangerous by-product may accumulate and thus aggravate the problem to be addressed by the actual drug.

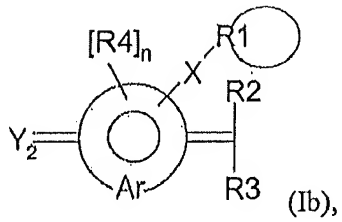
In contrast, in the prodrugs of the various embodiments of the present invention, the aromatic moiety is released only together with the polymer R1 (see, e.g., Figure 9 of Applicants' Specification).

Prodrugs according to formula (I) of the present invention release moieties of formula (Ia):



(Ia),

Prodrugs according to formula (II) of the present invention release moieties of formula (Ib):



(Ib),

wherein R1, R2, R3, R4, Y2, Ar, X and n are as defined in the Specification (the polymer moiety R1 is highlighted with a circle in each formula hereinabove).

The polymeric carrier moiety R1 bound to the small aromatic molecule provides shielding upon release and prevents the small aromatic molecule from exhibiting harmful properties. This is a significant difference and an advantage of the present invention over Greenwald.

One of ordinary skill in the art might expect such a polymer carrier R1 to cause steric hindrance interfering with the 1,(4+2p) elimination mechanism, so it would not have been obvious to synthesize the cascade prodrugs of the present invention with a reasonable expectation that they would work and indeed release the biologically active moiety.

Amir teaches prodrugs, similar to Greenwald, from which a small aromatic molecule, 1,4 quinone methide, is released (see, Amir, Scheme 1, compound 7). Again, such small aromatic molecules are highly undesired for pharmaceuticals.

Neither Finn nor Veronese remedies the deficiencies of the Greenwald/Amir combination. The combination of the Greenwald, Amir, Finn and Veronese documents would have led one of ordinary skill in the art to synthesize prodrugs from which problematic small aromatic molecules are released which - depending on their exact structure - could cause severe harm to patients.

Applicants respectfully submit that none of the cited references, nor any combination thereof, satisfies the criteria necessary to establish *prima facie* obviousness with respect to the claimed invention. Reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) are respectfully requested.

Double Patenting Rejections:

In the Office Action, the Examiner has set forth three (3) separate provisional obviousness-type double patenting rejections based on three co-pending patent applications. Specifically, the Examiner provisionally rejects the claims over claims 32-54 of co-pending U.S. Patent Application No. **12/663,628**; over claims 1-35 of co-pending U.S. Patent Application No. **12/865,693**; and over claims 1-36 of co-pending U.S. Patent Application No. **12/990,101**. Applicants respectfully defer addressing these provisional rejections until an indication of otherwise allowable subject matter is reached.

Nonetheless, Applicants respectfully submit that the instant application is the earliest filed of the four applications, and thus any obviousness-type double patenting rejection should properly be made in the later filed applications, and upon indication of otherwise allowable subject matter, withdrawn in this application, in accordance with standard Office procedureas indicated in the M.P.E.P. §804.I.B.1.

Conclusion:

Applicants respectfully submit that all pending claims patentably distinguish over the prior art of record. Reconsideration, withdrawal of the rejections and a Notice of Allowance are respectfully requested.

Respectfully submitted,

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(Date)

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